#298

Single-Dose and Steady-State Pharmacokinetics of MoxDuo™, a Dual-Opioid Formulation Containing a Fixed Ratio of Morphine and Oxycodone

Lynn Webster, MD;[1] Joel Owen, PhD, RPh;[2] Inger Darling, PhD;[3] Patricia Richards, MD, PhD;[4] Robin Kelen, RN;[4] and Warren Stern, PhD[4]

[1]Lifetree Clinical Research, Salt Lake City, Utah; [2]Union University, Jackson, Tennessee; [3]Cognigen Corporation, Buffalo, New York; [4]QRxPharma, Inc., Bedminster, New Jersey

Introduction

- Opioid analgesics are standard therapy for moderate to severe acute pain in many patients[1]
- Q8003 (MoxDuo™) is the first dual-opioid combination product that has been evaluated in clinical trials. MoxDuo immediate-release capsules were developed for the management of acute moderate to severe pain and contain morphine sulfate and oxycodone hydrochloride combined in a fixed ratio of 3:2 by weight
- The MoxDuo dosage forms currently being studied are 3/2 mg, 6/4 mg, 12/8 mg, and 18/12 mg
- Use of opioids in combination has been shown to be an effective therapeutic strategy that results in lower drug consumption and fewer side effects than monotherapy.[2-4] Moreover, MoxDuo may potentiate analgesia through interactions on a wider range of opioid subreceptors, including μ receptors (morphine) and κ receptors (oxycodone)[3-5]
- While the individual pharmacokinetic properties, including dose proportionality, of orally administered morphine and oxycodone are well documented,[6,7] the pharmacokinetics of a therapeutic product combining these opioids has not been reported. The aim of the present study is to assess the dose proportionality of MoxDuo by examining the single-dose (3 mg/2 mg and 12 mg/8 mg morphine/oxycodone, respectively) and steady-state (12 mg/8 mg) pharmacokinetic properties of MoxDuo

Objective

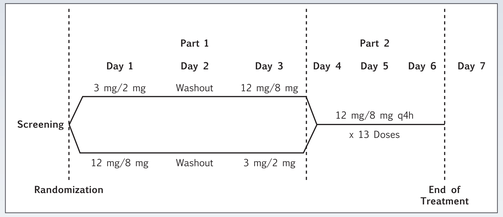
To assess the dose proportionality of the morphine plus oxycodone combination (MoxDuo) immediate-release capsule following single-dose administration of low-strength (3 mg/2 mg, morphine/oxycodone) and high-strength (12 mg/8 mg, morphine/oxycodone) MoxDuo capsules and to evaluate the steady-state pharmacokinetic profiles of MoxDuo after multiple-dose administration of the high-strength 12 mg/8 mg capsule

Methods

Study Design

- The study was performed in 18 healthy male and female volunteers
- Part 1 of the study was a single-dose, 2-way crossover study of a low-strength MoxDuo capsule containing 3 mg of morphine and 2 mg of oxycodone (3 mg/2 mg) and a high-strength MoxDuo capsule containing 12 mg of morphine and 8 mg of oxycodone (12 mg/8 mg) (**Figure 1**)
  - The first treatment was administered on the morning of day 1, followed by a 48-hour washout period
  - The second treatment was administered on the morning of day 3
- Part 2 of the study was a multiple-dose study of MoxDuo 12 mg/8 mg administered every 4 hours from the morning of day 4 until the morning of day 6 (total of 13 doses) (**Figure 1**)
  - Full-profile blood sampling was performed on days 1, 3, and 6
- In both part 1 and part 2, subjects received naltrexone 50-mg tablets at approximately 12 hours and at 30 minutes prior to each morning dose of MoxDuo
- All analyte concentrations for oxycodone, morphine, morphine-3β-o-glucuronide (M3G; a morphine metabolite), and morphine-6β-o-glucuronide (M6G; a morphine metabolite) were determined using high-performance liquid chromatography with tandem mass spectrometry (LC/MS/MS) detection by MEDTOX Labs, St. Paul, MN
- The detection limits for the assays were 50 pg/mL for oxycodone, 0.10 ng/mL for morphine, 2.0 ng/mL for morphine-3β-o-glucuronide (M3G; a morphine metabolite), and 0.5 ng/mL for morphine-6β-o-glucuronide (M6G; a morphine metabolite)

Figure 1. Study Design.



Subjects

- Subjects were healthy male and female volunteers (N=18), aged 18 to 55 years, inclusive
- Resting respiration rate was ≥10 breaths per minute, and the pulse oximetry measurement was ≥95%

Pharmacokinetic Evaluation

- The primary variables for the pharmacokinetic analysis were plasma concentrations of oxycodone, morphine, and the morphine metabolites M3G and M6G
- Pharmacokinetic analyses were performed using WinNonlin® Professional, Version 5.2 (Pharsight Corporation, Cary, NC)
- Standard noncompartmental analyses were conducted for computation of metrics of exposure (C_{max}, AUC) and disposition terminal elimination half-life ($t_{1/2}$)
- The accumulation index was calculated as the minimum plasma concentration (C_{min}) obtained under steady-state conditions (time 0 on day 6) divided by the C_{min} value obtained after a single dose (4-hour time point on day 1 or day 3)
- Analysis of variance (ANOVA) was performed using the general linear model procedure in SAS
  - Separate ANOVA analyses were performed to assess differences in the 3 mg/2 mg dose and the 12 mg/8 mg dose for each of the measured analytes (morphine, M3G, M6G, and oxycodone)
  - These analyses were performed for dose-normalized maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to 4 hours (AUC_{0-4}), area under the plasma concentration-time curve from time 0 to 8 hours (AUC_{0-8}), area under the plasma concentration-time curve from time 0 to the time of last non-zero concentration (AUC_{0-t}), and total area under the plasma concentration-time curve ($AUC_{0-\infty}$)
  - The ANOVA model included factors of sequence, subject nested within sequence, period, and treatment (formulation) on dose-normalized, log-transformed AUC and C_{max}
  - Ninety percent confidence intervals (CIs) of the ratios of the geometric means for C_{max}, AUC_{0-4}, AUC_{0-8}, AUC_{0-t}, and $AUC_{0-\infty}$ were compared with the equivalence criteria limits (80% and 125%)

Safety Evaluation

- Safety was assessed through the collection of adverse event (AE) reports, clinical laboratory evaluation, vital signs, and pulse oximetry
- Summary statistics were performed for measured values and change from screening values for each dose period, where applicable

Results

- Demographic and baseline characteristics are summarized in **Table 1**

Table 1. Subject Demographics

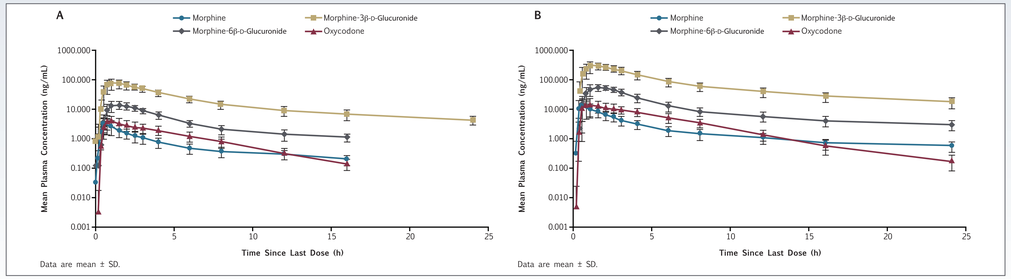
Characteristic	
Age, y	25.4 ± 6.8 (20.0-47.0)
Sex, n (%)	
Male	8 (44.4)
Female	10 (55.6)
Race, n (%)	
White	18 (100)
BMI, kg/m²	23.0 ± 2.5 (19.9-28.7)
Height, cm	173.0 ± 9.6 (154.8-194.2)
Weight, kg	69.3 ± 11.9 (55.8-95.3)

N=18.
BMI = body mass index.
All results are mean ± SD (range) unless otherwise noted.

MoxDuo Single-Dose Pharmacokinetic Results: Part 1

- All 18 subjects completed the study and were included in the descriptive statistics and the pairwise bioequivalence analyses, with the exception of 1 subject. This subject's day 3 M3G and M6G profiles were excluded because the predose M3G and M6G concentrations were greater than 5% of the corresponding C_{max} for that dosing interval
- The mean plasma concentrations for morphine, M3G, M6G, and oxycodone following administration of MoxDuo 3 mg/2 mg and 12 mg/8 mg are shown in **Figures 2A** and **2B**, respectively
- Mean plasma concentrations during the terminal phase for morphine and the metabolites (M3G and M6G) appeared to decline at similar rates for the 3 mg/2 mg dose (**Figure 2A**), resulting in apparent parallel profiles
- Similar parallel profiles for morphine, M3G, and M6G also were observed for the 12 mg/8 mg dose (**Figure 2B**)
- By inspection, the oxycodone profiles for the 3 mg/2 mg dose (**Figure 2A**) and the 12 mg/8 mg dose (**Figure 2B**) appeared to decline in a parallel manner

Figure 2. A) Plasma Concentrations for All Analytes After Administration of a Single Dose of MoxDuo 3 mg/2 mg; B) Plasma Concentrations for All Analytes After Administration of a Single Dose of MoxDuo 12 mg/8 mg.



Data are mean ± SD.

Data are mean ± SD.

- The plasma concentration vs time profiles for morphine, M3G, M6G, and oxycodone following administration of the 12 mg/8 mg dose were consistently approximately 4 times greater than those following administration of the 3 mg/2 mg dose, indicating pharmacokinetic linearity (dose proportionality) over this dose range (**Figures 2A** and **2B**)
- Peak exposure (C_{max}) and all metrics of total exposure (AUC) appear to be dose proportional across the two treatments (3 mg/2 mg and 12 mg/8 mg) (**Tables 2 & 3**)
- Terminal $t_{1/2}$ values were similar for M3G and M6G compared with morphine for both doses, consistent with the observed parallel decline of morphine, M3G, and M6G plasma concentrations[8,9]
  - The $t_{1/2}$ values for M3G and M6G were consistent with previously published results, however, due to more sensitive LC/MS/MS bioanalytical methods, the apparent $t_{1/2}$ value observed for morphine was substantially longer than those previously reported[8,9]
  - Time to maximum plasma concentration (T_{max}) values for morphine were similar to previously published results[9]
- The t_{max} and $t_{1/2}$ values for oxycodone were consistent with previous reports[10,11]

Table 2. Mean Dose-Normalized Values for Peak Exposure (C_{MAX}) and Disposition ($t_{1/2}$) Reported for Part 1

Analyte	Dose, mg	$t_{1/2}$, h	T_{max}, h	C_{max}, ng/mL	C_{max}/D, ng/mL/mg
Morphine (N=18)	3	8.77 ± 5.06	0.500 (0.330-2.50)	3.87 ± 1.46	1.29 ± 0.487
	12	10.5 ± 3.53	0.540 (0.330-3.00)	16.1 ± 7.51	1.34 ± 0.626
Morphine-3β-o-glucuronide (N=17)	3	9.49 ± 3.23	1.00 (0.750-3.00)	82.2 ± 18.8	27.4 ± 6.26
	12	9.52 ± 2.84	1.00 (0.500-3.00)	332 ± 58.0	27.6 ± 4.83
Morphine-6β-o-glucuronide (N=17)	3	8.60 ± 4.86	1.50 (0.750-3.00)	15.2 ± 3.11	5.08 ± 1.04
	12	10.9 ± 3.29	1.50 (1.00-3.00)	60.5 ± 7.47	5.04 ± 0.622
Oxycodone (N=18)	2	3.55 ± 0.738	1.00 (0.500-4.00)	4.89 ± 2.18	2.44 ± 1.09
	8	3.95 ± 0.515	1.00 (0.500-3.00)	17.8 ± 8.20	2.22 ± 1.03

C_{max} = maximum observed plasma concentration; C_{max}/D = dose-normalized maximum concentration; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration.
Data are mean ± SD for $t_{1/2}$ (h), C_{max}, and C_{max}/D and median (range) for T_{max} (h).

Table 3. Mean Dose-Normalized Values for Total Exposure (AUC) to Selected Time Points Reported for Part 1

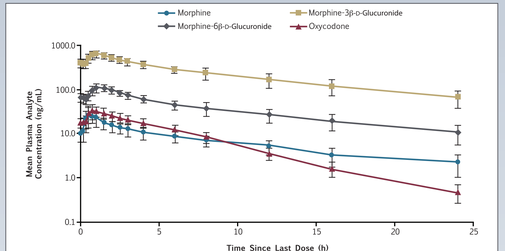
Analyte	Dose (mg)	AUC_{0-t}/Dose (ng·h/mL/mg)	AUC_{0-8}/Dose (ng·h/mL/mg)	AUC_{0-t}/Dose (ng·h/mL/mg)[b]	$AUC_{0-\infty}$/Dose (ng·h/mL/mg)
Morphine	3 (n=18)	2.07 ± 0.798	2.74 ± 0.977	2.47 ± 0.902	4.24 ± 1.97[b]
	12 (n=18)	2.09 ± 0.738	2.75 ± 0.853	2.48 ± 0.809	4.55 ± 1.17[c]
Morphine-3β-o-glucuronide	3 (n=17)	67.5 ± 16.8	98.2 ± 19.8	124 ± 25.0	157 ± 34.9
	12 (n=18)	66.9 ± 13.0	97.1 ± 17.7	123 ± 23.4	158 ± 29.3
Morphine-6β-o-glucuronide	3 (n=17)	12.1 ± 2.68	17.0 ± 3.06	19.3 ± 3.62	25.3 ± 6.23[b]
	12 (n=18)	11.8 ± 1.73	16.6 ± 2.28	18.8 ± 2.66	25.9 ± 4.53[b]
Oxycodone	2 (n=18)	5.06 ± 1.91	7.62 ± 2.75	9.20 ± 3.35	9.62 ± 3.55
	8 (n=18)	4.85 ± 1.78	7.50 ± 2.52	9.14 ± 3.02	9.62 ± 3.20

All results are mean ± SD.
[a]Time values for t in AUC_{0-t}/dose calculations were 6 hours for morphine, 16 hours for morphine-3β-o-glucuronide, 12 hours for morphine-6β-o-glucuronide, and 16 hours for oxycodone.
[b]n=16.
[c]n=15.
AUC = area under the plasma concentration-time curve; AUC_{0-4} = AUC from time 0 to 4 hours; AUC_{0-8} = AUC from time 0 to 8 hours; AUC_{0-t} = AUC from time 0 to the time of last non-zero concentration; $AUC_{0-\infty}$ = total area under the AUC.

Steady-State Pharmacokinetic Results: Part 2

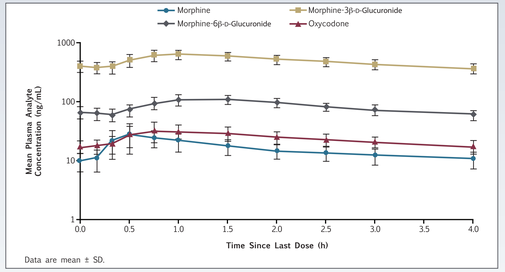
- Steady-state conditions for all analytes were reached prior to the day 6 dose administration (**Figures 3** and **4**)
  - This is most clearly illustrated in the 4 hour-dosing interval profile, where the pre-dose concentrations are similar to the 4-hour concentrations for each analyte (**Figure 4**)

Figure 3. Plasma Concentrations for All Analytes After Steady State Administration of MoxDuo 12 mg/8 mg (Full Profile)



Data are mean ± SD.

Figure 4. Plasma Concentrations for All Analytes After Steady State Administration of MoxDuo 12 mg/8 mg: Samples From Time 0 to 4 Hours (Dosing Interval)



Data are mean ± SD.

- Plasma concentration-time profiles from subjects administered the 12 mg/8 mg dose every 4 hours since day 4 show that day 6 morphine, M3G, and M6G plasma concentrations declined in a parallel manner, suggesting similar disposition (**Figure 3**)
- T_{max} values for all analytes were similar to those observed after a single-dose administration in part 1 of the study
- The accumulation index determined from the C_{min} values at steady state and after a single dose (4-hour point from Part 1) was 3.16 ± 0.927 for morphine, 2.59 ± 0.623 for M3G, 2.49 ± 0.618 for M6G, and 2.10 ± 0.319 for oxycodone

Bioequivalence Analysis of Pharmacokinetic Metrics From Part 1

- Results of pairwise statistical analyses of the dose-normalized pharmacokinetic parameter values between the low-strength 3 mg/2 mg capsule and the high-strength 12 mg/8 mg capsule in part 1 of the study are shown in **Table 4**

Table 4. Statistical Analyses of Dose-Normalized, Log-Transformed Pharmacokinetic Parameters for All Analytes Comparing Low-Strength (3 mg/2 mg) With High-Strength (12 mg/8 mg) MoxDuo Capsules

Analyte	PK Parameter	Point Estimate, %[a]	90% CI
Morphine	AUC_{0-4}	97.06	86.33-109.12
	AUC_{0-8}	97.87	89.81-106.65
	AUC_{0-t}	97.64	88.82-107.34
	$AUC_{0-\infty}$	92.07	84.26-100.59
	C_{max}	98.77	83.10-117.39
Morphine-3β-o-glucuronide	AUC_{0-4}	99.28	90.14-109.33
	AUC_{0-8}	100.42	94.01-107.27
	AUC_{0-t}	99.88	93.32-106.90
	$AUC_{0-\infty}$	99.60	92.44-107.32
	C_{max}	98.31	89.95-107.45
Morphine-6β-o-glucuronide	AUC_{0-4}	100.72	90.60-111.98
	AUC_{0-8}	102.37	94.61-110.77
	AUC_{0-t}	102.01	93.94-110.77
	$AUC_{0-\infty}$	96.00	86.70-106.29
	C_{max}	99.92	91.92-108.61
Oxycodone	AUC_{0-4}	102.48	92.40-113.66
	AUC_{0-8}	100.43	94.76-106.45
	AUC_{0-t}	99.38	94.04-105.03
	$AUC_{0-\infty}$	98.42	92.88-104.28
	C_{max}	109.62	97.47-123.28

[a]Point estimates of the ratios of the geometric means.
[b]The time values used for t in the AUC_{0-t} calculations were 6 hours for morphine, 16 hours for morphine-3β-o-glucuronide, 12 hours for morphine-6β-o-glucuronide, and 16 hours for oxycodone.
AUC = area under the plasma concentration-time curve; AUC_{0-4} = AUC from time 0 to 4 hours; AUC_{0-8} = AUC from time 0 to 8 hours; AUC_{0-t} = AUC from time 0 to the time of last non-zero concentration; $AUC_{0-\infty}$ = total area under the AUC; C_{max} = maximum observed plasma concentration; CI = confidence interval; PK = pharmacokinetic.

- Results show that the 90% CIs for all of the dose-normalized parameters for C_{max}, AUC_{0-4}, AUC_{0-8}, AUC_{0-t}, and $AUC_{0-\infty}$ are within the equivalence limits of 80% and 125% for all measured analytes
- The observation that all of the pharmacokinetic parameters fall within the equivalence limits for the 90% CIs provides conclusive evidence of dose proportionality between the 3 mg/2 mg dose and the 12 mg/8 mg dose
- A statistically significant difference in sex was found for oxycodone in dose-normalized, log-transformed AUC_{0-4}, AUC_{0-8}, AUC_{0-t}, and $AUC_{0-\infty}$, which were consistently higher in women than in men (41%-55% higher in women)
  - These sex differences were similar to those noted in a previous pharmacokinetic study[12]

Safety

- Oral doses of MoxDuo were well tolerated by healthy subjects. This was expected since all subjects received naltrexone prior to opioid dosing
  - Seven of the 18 subjects (38.9%) experienced a total of 14 treatment-emergent AEs
  - Eight events were mild in severity and 6 were moderate in severity; none were considered serious
  - The number of patients who experienced AEs related to MoxDuo are as follows: headache (3), dizziness (2), nausea (3), gastrointestinal pain (1), hyperhidrosis (1), and pallor (1)

Conclusions

- In the dual-opioid combination MoxDuo, morphine and oxycodone exhibit pharmacokinetic properties that are linear and dose proportional over a dosage range of 3 mg/2 mg to 12 mg/8 mg (morphine/oxycodone)
- Pharmacokinetic parameters for oxycodone, morphine, and morphine metabolites following administration of MoxDuo were consistent with results obtained for the individual drugs in previously published studies[8-11]
- Steady-state plasma concentrations for both morphine and oxycodone were achieved within 48 hours of MoxDuo administration
- Steady-state accumulation was observed for both morphine (approximately 3 times single dose C_{max}) and oxycodone (approximately 2 times single dose C_{max}) with administration of the 12 mg/8 mg dose every 4 hours
  - This low-level accumulation would be expected, considering the single-dose pharmacokinetics of morphine and oxycodone observed in the dual-opioid formula and the dosing interval
- Single-dose AUC values for oxycodone were higher in female subjects, as observed in a previous pharmacokinetic study[12]
- Both MoxDuo 3 mg/2 mg and 12 mg/8 mg were well tolerated (in naltrexone pretreated subjects)

References

1. Trescot AM et al. *Pain Physician.* 2008;11:S5-S62.
2. Blumenthal S et al. *Anesth Analg.* 2007;105:233-237.
3. Lauretti GR et al. *Br J Cancer.* 2003;89:2027-2030.
4. Ross FB et al. *Pain.* 2000;84:421-428.
5. Nielsen CK et al. *Pain.* 2007;132:289-300.
6. Lugo RA, Kern SE. *J Pain Palliat Care Pharmacother.* 2004;18:17-30.
7. Lugo RE, Kern SE. *J Pain Palliat Care Pharmacother.* 2002;16:5-18.
8. Osborne R et al. *Clin Pharmacol Ther.* 1990;47:12-19.
9. Gourlay GK et al. *Clin Pharmacol Ther.* 1989;46:463-468.
10. Lalovic B et al. *Clin Pharmacol Ther.* 2006;79:461-479.
11. Gammaitoni AR, Davis MW. *J Clin Pharmacol.* 2002;42:192-197.
12. Kaiko RF et al. *Clin Pharmacol Ther.* 1996;59:52-61.

Supported by QRxPharma, Bedminster, NJ, USA.

Presented at the 29th Annual Meeting of the American Pain Society, May 6-8, 2010, Baltimore, Maryland.

#298

Single-Dose and Steady-State Pharmacokinetics of MoxDuo™, a Dual-Opioid Formulation Containing a Fixed Ratio of Morphine and Oxycodone

Lynn Webster, MD;[1] Joel Owen, PhD, RPh;[2] Inger Darling, PhD;[3] Patricia Richards, MD, PhD;[4] Robin Kelen, RN;[4] and Warren Stern, PhD[4]

[1]Lifetree Clinical Research, Salt Lake City, Utah; [2]Union University, Jackson, Tennessee; [3]Cognigen Corporation, Buffalo, New York; [4]QRxPharma, Inc., Bedminster, New Jersey

Introduction

- Opioid analgesics are standard therapy for moderate to severe acute pain in many patients[1]
- Q8003 (MoxDuo™) is the first dual-opioid combination product that has been evaluated in clinical trials. MoxDuo immediate-release capsules were developed for the management of acute moderate to severe pain and contain morphine sulfate and oxycodone hydrochloride combined in a fixed ratio of 3:2 by weight
- The MoxDuo dosage forms currently being studied are 3/2 mg, 6/4 mg, 12/8 mg, and 18/12 mg
- Use of opioids in combination has been shown to be an effective therapeutic strategy that results in lower drug consumption and fewer side effects than monotherapy.[2-4] Moreover, MoxDuo may potentiate analgesia through interactions on a wider range of opioid subreceptors, including μ receptors (morphine) and κ receptors (oxycodone)[3-5]
- While the individual pharmacokinetic properties, including dose proportionality, of orally administered morphine and oxycodone are well documented,[6,7] the pharmacokinetics of a therapeutic product combining these opioids has not been reported. The aim of the present study is to assess the dose proportionality of MoxDuo by examining the single-dose (3 mg/2 mg and 12 mg/8 mg morphine/oxycodone, respectively) and steady-state (12 mg/8 mg) pharmacokinetic properties of MoxDuo

Objective

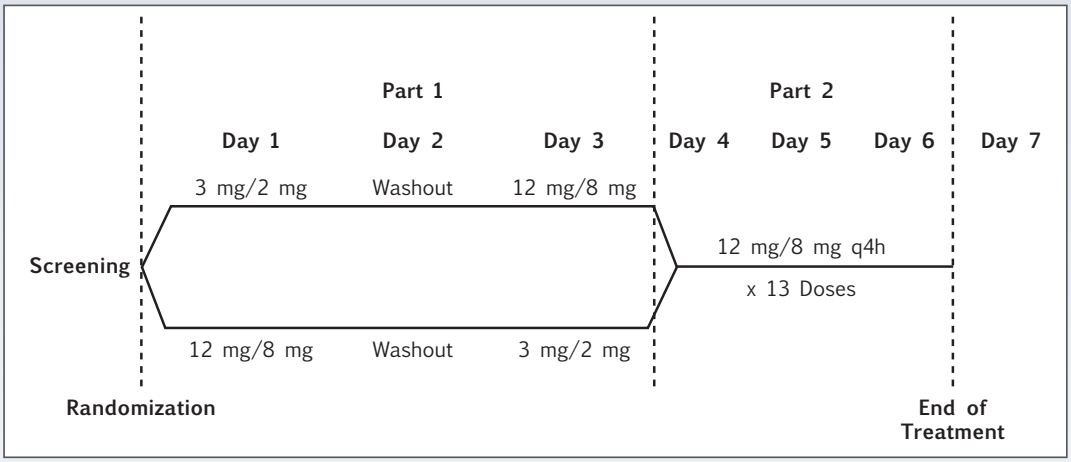
To assess the dose proportionality of the morphine plus oxycodone combination (MoxDuo) immediate-release capsule following single-dose administration of low-strength (3 mg/2 mg, morphine/oxycodone) and high-strength (12 mg/8 mg, morphine/oxycodone) MoxDuo capsules and to evaluate the steady-state pharmacokinetic profiles of MoxDuo after multiple-dose administration of the high-strength 12 mg/8 mg capsule

Methods

Study Design

- The study was performed in 18 healthy male and female volunteers
- Part 1 of the study was a single-dose, 2-way crossover study of a low-strength MoxDuo capsule containing 3 mg of morphine and 2 mg of oxycodone (3 mg/2 mg) and a high-strength MoxDuo capsule containing 12 mg of morphine and 8 mg of oxycodone (12 mg/8 mg) (**Figure 1**)
  - The first treatment was administered on the morning of day 1, followed by a 48-hour washout period
  - The second treatment was administered on the morning of day 3
- Part 2 of the study was a multiple-dose study of MoxDuo 12 mg/8 mg administered every 4 hours from the morning of day 4 until the morning of day 6 (total of 13 doses) (**Figure 1**)
  - Full-profile blood sampling was performed on days 1, 3, and 6
- In both part 1 and part 2, subjects received naltrexone 50-mg tablets at approximately 12 hours and at 30 minutes prior to each morning dose of MoxDuo
- All analyte concentrations for oxycodone, morphine, morphine-3β-D-glucuronide (M3G; a morphine metabolite), and morphine-6β-D-glucuronide (M6G; a morphine metabolite) were determined using high-performance liquid chromatography with tandem mass spectrometry [LC/MS/MS]) detection by MEDTOX Labs, St. Paul, MN
- The detection limits for the assays were 50 pg/mL for oxycodone, 0.10 ng/mL for morphine, 2.0 ng/mL for morphine-3β-D-glucuronide (M3G; a morphine metabolite), and 0.5 ng/mL for morphine-6β-D-glucuronide (M6G; a morphine metabolite)

Figure 1. Study Design.



Subjects

- Subjects were healthy male and female volunteers (N=18), aged 18 to 55 years, inclusive
- Resting respiration rate was ≥10 breaths per minute, and the pulse oximetry measurement was ≥95%

Pharmacokinetic Evaluation

- The primary variables for the pharmacokinetic analysis were plasma concentrations of oxycodone, morphine, and the morphine metabolites M3G and M6G
- Pharmacokinetic analyses were performed using WinNonlin® Professional, Version 5.2 (Pharsight Corporation, Cary, NC)
- Standard noncompartmental analyses were conducted for computation of metrics of exposure (C_{max}, AUC) and disposition terminal elimination half-life ($t_{1/2}$)
- The accumulation index was calculated as the minimum plasma concentration (C_{min}) obtained under steady-state conditions (time 0 on day 6) divided by the C_{min} value obtained after a single dose (4-hour time point on day 1 or day 3)
- Analysis of variance (ANOVA) was performed using the general linear model procedure in SAS
  - Separate ANOVA analyses were performed to assess differences in the 3 mg/2 mg dose and the 12 mg/8 mg dose for each of the measured analytes (morphine, M3G, M6G, and oxycodone)

- These analyses were performed for dose-normalized maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to 4 hours (AUC_{0-4}), area under the plasma concentration-time curve from time 0 to 8 hours (AUC_{0-8}), area under the plasma concentration-time curve from time 0 to the time of last non-zero concentration (AUC_{0-t}), and total area under the plasma concentration-time curve ($AUC_{0-\infty}$)

– The ANOVA model included factors of sequence, subject nested within sequence, period, and treatment (formulation) on dose-normalized, log-transformed AUC and C_{max}

– Ninety percent confidence intervals (CIs) of the ratios of the geometric means for C_{max}, AUC_{0-4}, AUC_{0-8}, AUC_{0-t}, and $AUC_{0-\infty}$ were compared with the equivalence criteria limits (80% and 125%)

Safety Evaluation

- Safety was assessed through the collection of adverse event (AE) reports, clinical laboratory evaluation, vital signs, and pulse oximetry
- Summary statistics were performed for measured values and change from screening values for each dose period, where applicable

Results

- Demographic and baseline characteristics are summarized in **Table 1**

Table 1. Subject Demographics

Characteristic	
Age, y	25.4 ± 6.8 (20.0-47.0)
Sex, n (%)	
Male	8 (44.4)
Female	10 (55.6)
Race, n (%)	
White	18 (100)
BMI, kg/m²	23.0 ± 2.5 (19.9-28.7)
Height, cm	173.0 ± 9.6 (154.8-194.2)
Weight, kg	69.3 ± 11.9 (55.8-95.3)

N=18.
BMI = body mass index.
All results are mean ± SD (range) unless otherwise noted.

MoxDuo Single-Dose Pharmacokinetic Results: Part 1

- All 18 subjects completed the study and were included in the descriptive statistics and the pairwise bioequivalence analyses, with the exception of 1 subject. This subject's day 3 M3G and M6G profiles were excluded because the predose M3G and M6G concentrations were greater than 5% of the corresponding C_{max} for that dosing interval
- The mean plasma concentrations for morphine, M3G, M6G, and oxycodone following administration of MoxDuo 3 mg/2 mg and 12 mg/8 mg are shown in **Figures 2A** and **2B**, respectively
- Mean plasma concentrations during the terminal phase for morphine and the metabolites (M3G and M6G) appeared to decline at similar rates for the 3 mg/2 mg dose (**Figure 2A**), resulting in apparent parallel profiles
- Similar parallel profiles for morphine, M3G, and M6G also were observed for the 12 mg/8 mg dose (**Figure 2B**)
- By inspection, the oxycodone profiles for the 3 mg/2 mg dose (**Figure 2A**) and the 12 mg/8 mg dose (**Figure 2B**) appeared to decline in a parallel manner

- The plasma concentration vs time profiles for morphine, M3G, M6G, and oxycodone following administration of the 12 mg/8 mg dose were consistently approximately 4 times greater than those following administration of the 3 mg/2 mg dose, indicating pharmacokinetic linearity (dose proportionality) over this dose range (**Figures 2A** and **2B**)
- Peak exposure (C_{max}) and all metrics of total exposure (AUC) appear to be dose proportional across the two treatments (3 mg/2 mg and 12 mg/8 mg) (**Tables 2** & **3**)
- Terminal $t_{1/2}$ values were similar for M3G and M6G compared with morphine for both doses, consistent with the observed parallel decline of morphine, M3G, and M6G plasma concentrations[8,9]
  - The $t_{1/2}$ values for M3G and M6G were consistent with previously published results, however, due to more sensitive LC/MS/MS bioanalaytical methods, the apparent $t_{1/2}$ value observed for morphine was substantially longer than those previously reported[8,9]
  - Time to maximum plasma concentration (T_{max}) values for morphine were similar to previously published results[9]
- The t_{max} and $t_{1/2}$ values for oxycodone were consistent with previous reports[10,11]

Table 2. Mean Dose-Normalized Values for Peak Exposure (C_{max}) and Disposition ($T_{1/2}$) Reported for Part 1

Analyte	Dose, mg	$t_{1/2}$, h	T_{max}, h	C_{max}, ng/mL	C_{max}/D, ng/mL/mg
Morphine (N=18)	3	8.77 ± 5.06	0.500 (0.330-2.50)	3.87 ± 1.46	1.29 ± 0.487
	12	10.5 ± 3.53	0.540 (0.330-3.00)	16.1 ± 7.51	1.34 ± 0.626
Morphine-3β-D-glucuronide (N=17)	3	9.49 ± 3.23	1.00 (0.750-3.00)	82.2 ± 18.8	27.4 ± 6.26
	12	9.52 ± 2.84	1.00 (0.500-3.00)	332 ± 58.0	27.6 ± 4.83
Morphine-6β-D-glucuronide (N=17)	3	8.60 ± 4.86	1.50 (0.750-3.00)	15.2 ± 3.11	5.08 ± 1.04
	12	10.9 ± 3.29	1.50 (1.00-3.00)	60.5 ± 7.47	5.04 ± 0.622
Oxycodone (N=18)	2	3.55 ± 0.738	1.00 (0.500-4.00)	4.89 ± 2.18	2.44 ± 1.09
	8	3.95 ± 0.515	1.00 (0.500-3.00)	17.8 ± 8.20	2.22 ± 1.03

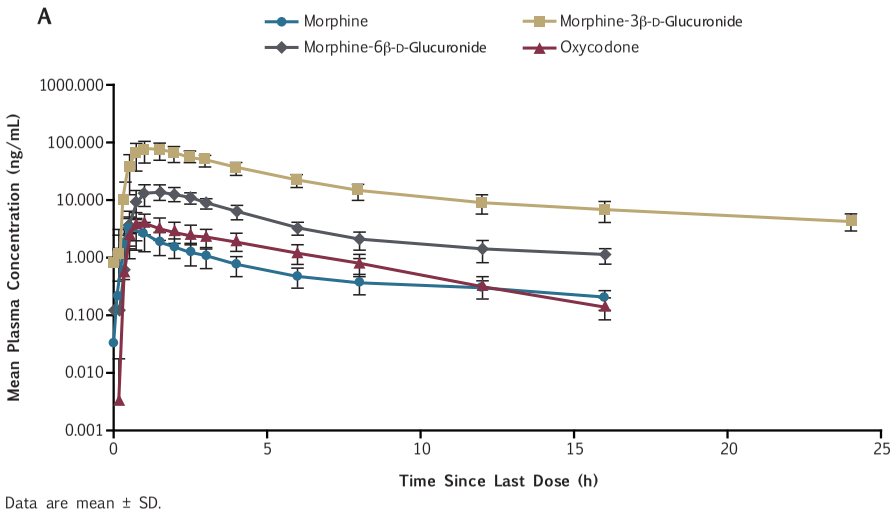
C_{max} = maximum observed plasma concentration; C_{max}/D = dose-normalized maximum concentration; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration.
Data are mean ± SD for $t_{1/2}$ (h), C_{max}, and C_{max}/D and median (range) for T_{max} (h).

Table 3. Mean Dose-Normalized Values for Total Exposure (AUC) to Selected Time Points Reported for Part 1

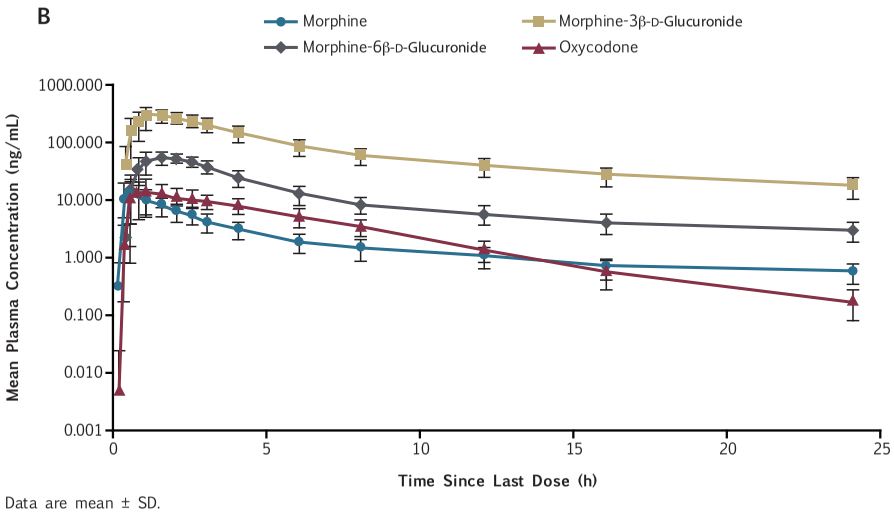
Analyte	Dose (mg)	AUC_{0-4}/Dose (ng·h/mL/mg)	AUC_{0-8}/Dose (ng·h/mL/mg)	AUC_{0-t}/Dose (ng·h/mL/mg)[a]	$AUC_{0-\infty}$/Dose (ng·h/mL/mg)
Morphine	3 (n=18)	2.07 ± 0.798	2.74 ± 0.977	2.47 ± 0.902	4.24 ± 1.97[b]
	12 (n=18)	2.09 ± 0.738	2.75 ± 0.853	2.48 ± 0.809	4.55 ± 1.17[c]
Morphine-3β-D-glucuronide	3 (n=17)	67.5 ± 16.8	98.2 ± 19.8	124 ± 25.0	157 ± 34.9
	12 (n=18)	66.9 ± 13.0	97.1 ± 17.7	123 ± 23.4	158 ± 29.3
Morphine-6β-D-glucuronide	3 (n=17)	12.1 ± 2.68	17.0 ± 3.06	19.3 ± 3.62	25.3 ± 6.23[b]
	12 (n=18)	11.8 ± 1.73	16.6 ± 2.28	18.8 ± 2.66	25.9 ± 4.53[b]
Oxycodone	2 (n=18)	5.06 ± 1.91	7.62 ± 2.75	9.20 ± 3.35	9.62 ± 3.55
	8 (n=18)	4.85 ± 1.78	7.50 ± 2.52	9.14 ± 3.02	9.62 ± 3.20

All results are mean ± SD.
[a]Time values for t in AUC_{0-t}/dose calculations were 6 hours for morphine, 16 hours for morphine-3β-D-glucuronide, 12 hours for morphine-6β-D-glucuronide, and 16 hours for oxycodone.
[b]n=16.
[c]n=15.
AUC = area under the plasma concentration-time curve; AUC_{0-4} = AUC from time 0 to 4 hours; AUC_{0-8} = AUC from time 0 to 8 hours; AUC_{0-t} = AUC from time 0 to the time of last non-zero concentration; $AUC_{0-\infty}$ = total area under the AUC.

Figure 2. A) Plasma Concentrations for All Analytes After Administration of a Single Dose of MoxDuo 3 mg/2 mg; B) Plasma Concentrations for All Analytes After Administration of a Single Dose of MoxDuo 12 mg/8 mg.



Data are mean ± SD.

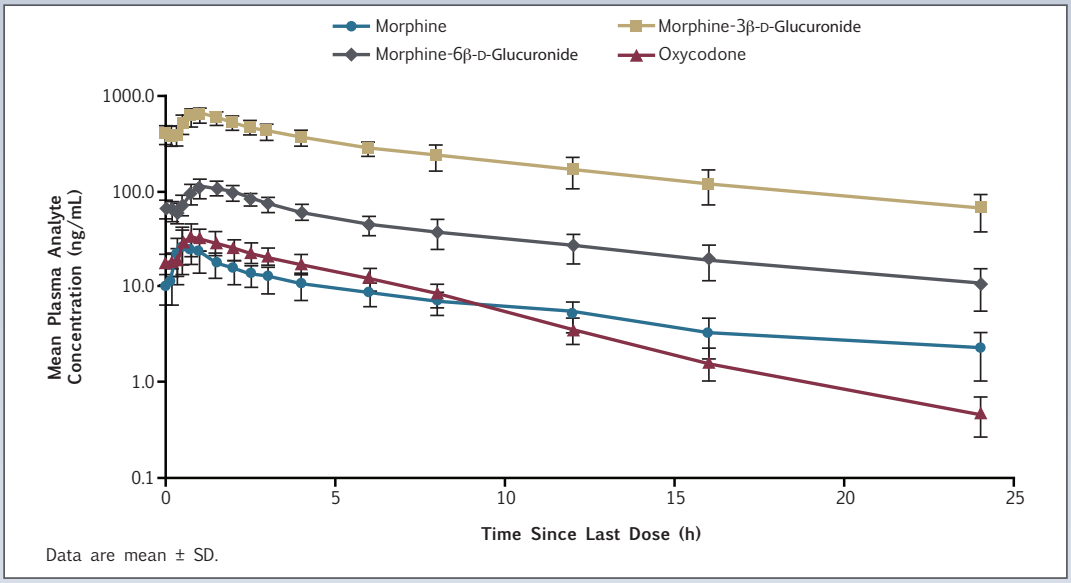


Data are mean ± SD.

Steady-State Pharmacokinetic Results: Part 2

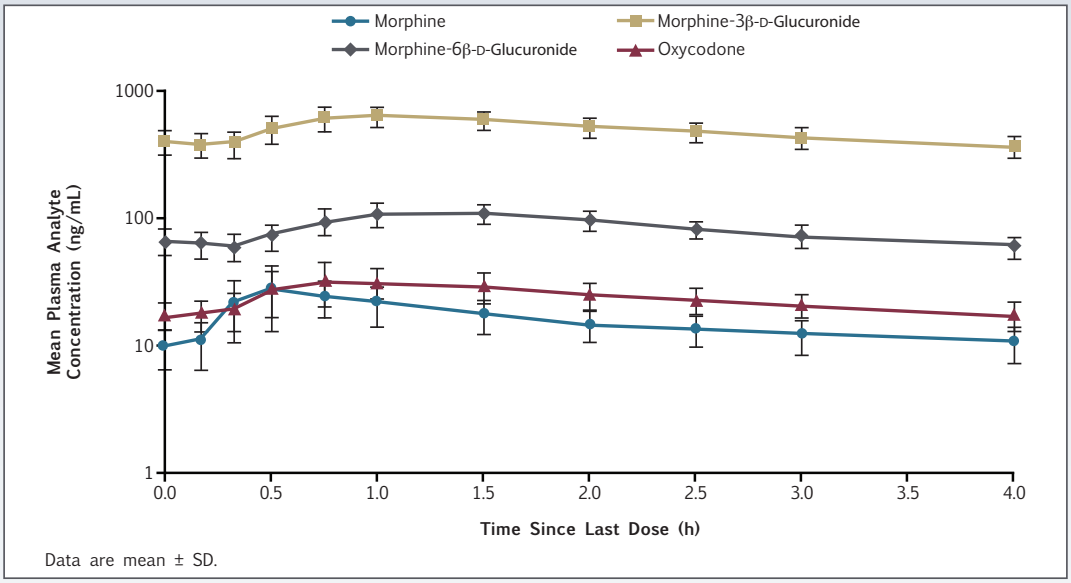
- Steady-state conditions for all analytes were reached prior to the day 6 dose administration (**Figures 3** and **4**)
  - This is most clearly illustrated in the 4 hour-dosing interval profile, where the pre-dose concentrations are similar to the 4-hour concentrations for each analyte (**Figure 4**)

Figure 3. Plasma Concentrations for All Analytes After Steady State Administration of MoxDuo 12 mg/8 mg (full profile)



Data are mean ± SD.

Figure 4. Plasma Concentrations for All Analytes After Steady State Administration of MoxDuo 12 mg/8 mg: Samples From Time 0 to 4 Hours (dosing interval)



Data are mean ± SD.

- Plasma concentration-time profiles from subjects administered the 12 mg/8 mg dose every 4 hours since day 4 show that day 6 morphine, M3G, and M6G plasma concentrations declined in a parallel manner, suggesting similar disposition (**Figure 3**)
- T_{max} values for all analytes were similar to those observed after a single-dose administration in part 1 of the study
- The accumulation index determined from the C_{min} values at steady state and after a single dose (4-hour point from Part 1) was 3.16 ± 0.927 for morphine, 2.59 ± 0.623 for M3G, 2.49 ± 0.618 for M6G, and 2.10 ± 0.319 for oxycodone

Bioequivalence Analysis of Pharmacokinetic Metrics From Part 1

- Results of pairwise statistical analyses of the dose-normalized pharmacokinetic parameter values between the low-strength 3 mg/2 mg capsule and the high-strength 12 mg/8 mg capsule in part 1 of the study are shown in **Table 4**

Table 4. Statistical Analyses of Dose-Normalized, Log-Transformed Pharmacokinetic Parameters for All Analytes Comparing Low-Strength (3 mg/2 mg) With High-Strength (12 mg/8 mg) MoxDuo Capsules

Analyte	PK Parameter	Point Estimate, %[a]	90% CI
Morphine	AUC_{0-4}	97.06	86.33-109.12
	AUC_{0-8}	97.87	89.81-106.65
	AUC_{0-t}[b]	97.64	88.82-107.34
	$AUC_{0-\infty}$	92.07	84.26-100.59
	C_{max}	98.77	83.10-117.39
Morphine-3β-D-glucuronide	AUC_{0-4}	99.28	90.14-109.33
	AUC_{0-8}	100.42	94.01-107.27
	AUC_{0-t}[b]	99.88	93.32-106.90
	$AUC_{0-\infty}$	99.60	92.44-107.32
	C_{max}	98.31	89.95-107.45
Morphine-6β-D-glucuronide	AUC_{0-4}	100.72	90.60-111.98
	AUC_{0-8}	102.37	94.61-110.77
	AUC_{0-t}[b]	102.01	93.94-110.77
	$AUC_{0-\infty}$	96.00	86.70-106.29
	C_{max}	99.92	91.92-108.61
Oxycodone	AUC_{0-4}	102.48	92.40-113.66
	AUC_{0-8}	100.43	94.76-106.45
	AUC_{0-t}[b]	99.38	94.04-105.03
	$AUC_{0-\infty}$	98.42	92.88-104.28
	C_{max}	109.62	97.47-123.28

[a]Point estimates of the ratios of the geometric means.
[b]The time values used for t in the AUC_{0-t} calculations were 6 hours for morphine, 16 hours for morphine-3β-D-glucuronide, 12 hours for morphine-6β-D-glucuronide, and 16 hours for oxycodone.
AUC = area under the plasma concentration-time curve; AUC_{0-4} = AUC from time 0 to 4 hours; AUC_{0-8} = AUC from time 0 to 8 hours; AUC_{0-t} = AUC from time 0 to the time of last non-zero concentration; $AUC_{0-\infty}$ = total area under the AUC; C_{max} = maximum observed plasma concentration; CI = confidence interval; PK = pharmacokinetic.

- Results show that the 90% CIs for all the dose-normalized parameters for C_{max}, AUC_{0-4}, AUC_{0-8}, AUC_{0-t}, and $AUC_{0-\infty}$ are within the equivalence limits of 80% and 125% for all measured analytes
- The observation that all of the pharmacokinetic parameters fall within the equivalence limits for the 90% CIs provides conclusive evidence of dose proportionality between the 3 mg/2 mg dose and the 12 mg/8 mg dose
- A statistically significant difference in sex was found for oxycodone in dose-normalized, log-transformed AUC_{0-4}, AUC_{0-8}, AUC_{0-t}, and $AUC_{0-\infty}$, which were consistently higher in women than in men (41%-55% higher in women)
  - These sex differences were similar to those noted in a previous pharmacokinetic study[12]

Safety

- Oral doses of MoxDuo were well tolerated by healthy subjects. This was expected since all subjects received naltrexone prior to opioid dosing
  - Seven of the 18 subjects (38.9%) experienced a total of 14 treatment-emergent AEs
  - Eight events were mild in severity and 6 were moderate in severity; none were considered serious
  - The number of patients who experienced AEs related to MoxDuo are as follows: headache (3), dizziness (2), nausea (3), gastrointestinal pain (1), hyperhidrosis (1), and pallor (1)

Conclusions

- In the dual-opioid combination MoxDuo, morphine and oxycodone exhibit pharmacokinetic properties that are linear and dose proportional over a dosage range of 3 mg/2 mg to 12 mg/8 mg (morphine/oxycodone)
- Pharmacokinetic parameters for oxycodone, morphine, and morphine metabolites following administration of MoxDuo were consistent with results obtained for the individual drugs in previously published studies[8-11]
- Steady-state plasma concentrations for both morphine and oxycodone were achieved within 48 hours of MoxDuo administration
- Steady-state accumulation was observed for both morphine (approximately 3 times single dose C_{min}) and oxycodone (approximately 2 times single dose C_{min}) with administration of the 12 mg/8 mg dose every 4 hours
  - This low-level accumulation would be expected, considering the single-dose pharmacokinetics of morphine and oxycodone observed in the dual-opioid formula and the dosing interval
- Single-dose AUC values for oxycodone were higher in female subjects, as observed in a previous pharmacokinetic study[12]
- Both MoxDuo 3 mg/2 mg and 12 mg/8 mg were well tolerated (in naltrexone pretreated subjects)

References

1. Trescot AM et al. *Pain Physician.* 2008;11:S5-S62.
2. Blumenthal S et al. *Anesth Analg.* 2007;105:233-237.
3. Lauretti GR et al. *Br J Cancer.* 2003;89:2027-2030.
4. Ross FB et al. *Pain.* 2000;84:421-428.
5. Nielsen CK et al. *Pain.* 2007;132:289-300.
6. Lugo RA, Kern SE. *J Pain Palliat Care Pharmacother.* 2004;18:17-30.
7. Lugo RE, Kern SE. *J Pain Palliat Care Pharmacother.* 2002;16:5-18.
8. Osborne R et al. *Clin Pharmacol Ther.* 1990;47:12-19.
9. Gourlay GK et al. *Clin Pharmacol Ther.* 1989;46:463-468.
10. Lalovic B et al. *Clin Pharmacol Ther.* 2006;79:461-479.
11. Gammaitoni AR, Davis MW. *J Clin Pharmacol.* 2002;42:192-197.
12. Kaiko RF et al. *Clin Pharmacol Ther.* 1996;59:52-61.

Supported by QRxPharma, Bedminster, NJ, USA.

Presented at the 29th Annual Meeting of the American Pain Society, May 6-8, 2010, Baltimore, Maryland.